MR SPECTROSCOPY GUIDED BRAIN TUMOR DETECTION AND EVALUATION USING FUZZY CLUSTERING*

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Abstract- **Magnetic Resonance Spectroscopic Imaging (MRSI) is a non-invasive method that provides biochemical information about the tissue. Research studies have shown that proton MRSI metabolites (N-acetyl aspartate, Choline, Creatine, Lipid/Lactate) have the potential to be used in differentiating brain tumors from normal tissues. In this work, an unsupervised classifier based on Cho/NAA and NAA/Cr ratios was developed to detect 4 different tumor types in 20 patients. The segmentation results were consistent with the defected anatomical regions of the anatomical MRI in most cases. Abnormal regions contained higher Cho/Cr and Cho/NAA (1.95, 2.05) than normal ones (1.10, 0.63) but their NAA/Cr was lower (1.36 vs. 2.08). The mean values of Cho/Cr, Cho/NAA, and NAA/Cr in contralateral normal tissues (1.10, 0.63, 2.08) were consistent with (1.14, 0.79, 1.39) reported in the literature. Different logistic regression models were developed to evaluate feature performance. Statistical analysis of the results showed that Cho/NAA was the most discriminating feature for differentiating tumors from normal tissues (P<0.001, Odd Ratio=19.12).**

I. INTRODUCTION

Characteristics of brain tumors have high influence on their treatment. Biopsy, an invasive tool, is the gold standard for diagnosis of the brain tumors type or grade while non-invasive techniques are preferred. Magnetic Resonance Spectroscopic Imaging (MRSI) is a non-invasive technique which has shown high potential in characterizing brain tumors [1]-[10]. It reflects biochemical properties of the tissue. Proton MRSI (H-MRSI) metabolite signals are obtained by utilizing radiofrequency excitation in conjunction with magnetic field [1]. Different metabolites resonance in different frequencies based on their chemical environments which make them distinguishable [1]. The MRSI signal provides useful information about N-acetyl aspartate (NAA), Choline (Cho), Creatine (Cr), and Lipid-Lactate (Lip-Lac) metabolites of the tissue that are mostly used for brain abnormality detection [1]. The investigations in [1]-[4] have shown that metabolite peaks like Cho, Lip-Lac and ratios like Cho/Cr are helpful in determining the tumor type and grade. The Cho, Lip-Lac, and Cho/Cr are higher in high grade tumors than low grade ones. In another attempt, the H-MRSI role in differentiating tumor from radiation necrosis has been evaluated [5]-[6]. It was shown that Cho/Cr and Cho/NAA were higher in tumor than in radiation necrosis and normal appearing white matter. According to histopathologic findings, Cho is involved in membrane construction, so it increases in tumors because of cell proliferation [1]. NAA is contained in neurons and axons, so it decreases in tumor because of axon defects [1].

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Cr takes part in energy production, so it is expected to decrease in tumor because of energy exhaustion although this is less supported by experimental data [1].

Based on MRSI's potentials in differentiating brain tumor types and grades, different pattern analysis methods have been proposed for supervised/unsupervised brain tumor classification to aid physicians in their diagnoses [7]-[10]. A supervised classifier like Neural Network [9] or an unsupervised classifier like a fuzzy c-means [10] perform the classification based on metabolite peaks characteristics [7] or wavelet coefficients [8], [10]. Supervised classifiers in contrast to the unsupervised ones need training to be able to differentiate abnormal parts from normal tissues. Due to difficulties with the training sets, an unsupervised classifier is a better choice.

The aim of this work is to develop an unsupervised classifier based on MRSI findings to differentiate various types of tumors and normal tissues non-invasively and compare the brain tumors MRSI characteristics to those of the normal tissues.

II. METHODOLOGY

In this work, 20 patients (29 slices: 1 or 2 slice per patient): 4 females and 16 males ages 19-69 were studied. They were affected by Glioblastoma multiforme (GBM, n=8), Oligodenroglioma (n=4), Astrocytoma (n=7) and OligoAstrocytoma (n=1). The MRSI were acquired on a 3 T GE Signa System using 2D CSI (32×32 matrix) H-MRSI pulse sequences. T2-Weighted MRI was also available for all patients. MRSI signals were processed using Eigntool image analysis software (Henry Ford Health System, Detroit, MI) [12]. The normalized metabolites with respect to normal Creatine (nCr) (NAA/nCr, Cho/nCr, Cr/nCr, Lip-Lac/nCr) and the Cho/Cr, Cho/NAA and NAA/Cr ratios were computed for each slice.

First, the metabolite maps were registered to the T2-weighted MRI in order to compare the detected abnormality location with its anatomical reference. It has been shown that fuzzy C-means clustering (FCM), an unsupervised classifier, offers promising results in brain abnormality detection [10]. Thus, it was applied to normalized features in order to classify image voxels into four classes: background, cancerous, partial volume region around the brain, and normal. The results showed that the abnormal region was more concentrated in the cancerous cluster by choosing four classes versus three ones. Different sets of MRSI ratios were tested in order to find the best. The detected abnormality locations were compared with the anatomical images in each case to evaluate the selected ratios. The Cho/NAA and NAA/Cr ratios performed the best to detect abnormal regions. According to references [1]-[6], the Cho/NAA ratio is higher

in tumor than in normal tissue, so the cancerous cluster is chosen as the cluster with the highest Cho/NAA mean value (cluster center). Then, the abnormal lesion in the cancerous cluster should be detected. Tumors had mostly circular shapes in our cases, so a circular Hough transform [13] was applied to the cancerous cluster in order to detect tumor like regions. The highest intensity was found in the region with the highest similarity to the circle.

Hough transform considers global relationships between pixels and connects points if they form a specified shape [13]. In this study, the desired shape was specified as follow:

$$(x-c_1)^2+(y-c_2)^2=c_3^{\,2} \quad (1)$$

where x, y are the location of pixels and c_1, c_2, c_3 are the variables. After some trial and errors, we set c_3 to 10 pixels to focus on the circular regions with moderate size. The curve definition in (1) can be extended to detect ellipsoid like shapes in the cancerous cluster.

At last, the Cho/NAA values of the tumor like regions were compared with that of the contralateral side. The region with the highest difference was the tumor. To this end, the vertical axis of the brain was detected using Hotelling transform [13] in order to specify the contralateral points as the mirror of the abnormal part with respect to the vertical brain axis. Hotelling transform is based on principle component concept to detect perependicular axes of a 2D object. A threshold equal to mean values of pixel intensities was set to separate brain (object) from background. The perpendicular axes were the two eigenvectors of the covariance matrix of the object (brain). The algorithm procedure in abnormality detection is shown in Fig. 1 for a glioblastoma multiforme (GBM) patient.

Comparing with figures reported in [5], we evaluated the MRSI features of the detected abnormalities and normal tissues numerically (Table I). Three logistic regression models were developed to evaluate the MRSI features in differentiation of tumors from normal tissues statistically. The odd ratios and P-values are reported in Table II. The features with P-values less than 0.01 are considered as the most significant ones.

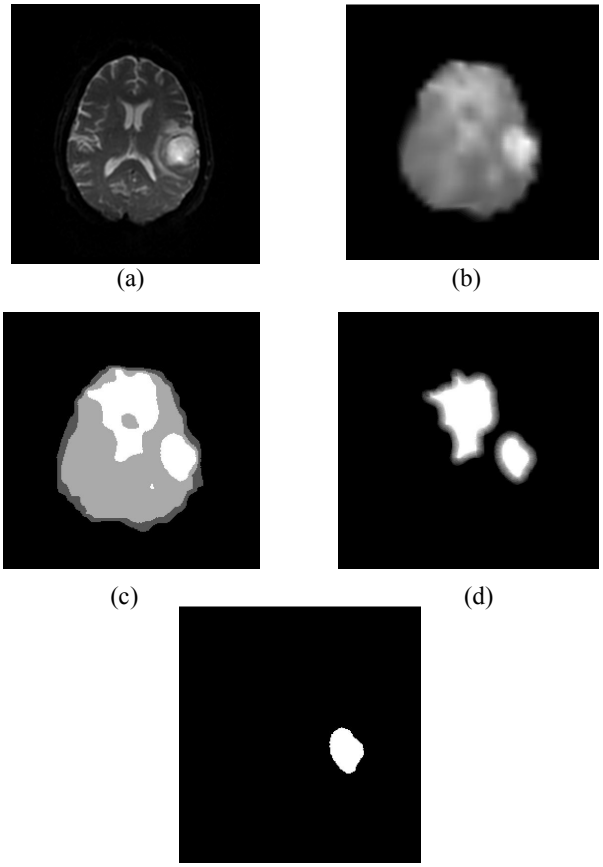

Fig. 1. A 60 year-old woman with surgically proven left posterior temporal GlioBlastoma Multiforme (GBM): a) T2-weighted image, b) Cho/Cr ratio metabolite map, c) clustering results in 4 different intensities (background=0, partial volume region around the brain =10, normal =20, cancerous=30), d) Hough transform result on the cancerous cluster, e) The detected tumor after Cho/NAA comparison of the two sides.

III. Results

Brain tumors were detected based on FCM clustering of the Cho/NAA and NAA/Cr images and shapes of the identified regions. The detected abnormal regions were compared with the anatomical images to evaluate the results. The proposed method could detect the abnormal regions in all but two cases.

The first one was a low grade tumor with low contrast in Cho/NAA and NAA/Cr ratio images. In the second one, there was extensive necrosis appearing dark in Cho/NAA and thus the algorithm could not detect the abnormal region.

After detecting the abnormal region, the MRSI features of voxels with the highest possibility of being cancerous (their membership values more than 0.78) were evaluated. The mean values and ranges of Cho/Cr, Cho/NAA, and NAA/Cr of the detected tumor regions and their contralateral normal ones are reported in Table I. As shown, these values are in good agreement with those in the literature. As expected, Cho/NAA and Cho/Cr had higher mean values in tumor than in normal regions. On the other hand, the NAA/Cr was lower in tumor than in normal regions. The boxplot comparison of Cho/Cr, NAA/Cr, and Cho/NAA are shown in Fig. 2. The Cho/Cr and Cho/NAA covered larger ranges while NAA/Cr included lower ones in tumor vs. normal tissues. Three different logistic regression models were developed based on Cho/Cr, Cho/NAA, and NAA/Cr to evaluate features statistically in differentiation of tumors from normal tissues. The mean values were used to dichotomized features for developing univariate logistic regression models.

Table I
The mean values and ranges of MRSI ratios in tumor and normal tissues detected by proposed algorithm in comparison with [5].

Ratio	Tumor	Tumor [5]	Normal	Normal [5]
Cho/Cr	1.95 (0.85-4.39)	2.52 (1.66-4.26)	1.10 (0.81-2.05)	1.14 (0.86-1.59)
NAA/Cr	1.36 (0.37-3.88)	0.79 (0.47-1.15)	2.08 (0.75-6.00)	1.39 (0.64-2.00)
Cho/NAA	2.05 (0.57-6.45)	3.48 (1.70-6.47)	0.63 (0.27-1.85)	0.79 (0.56-1.20)

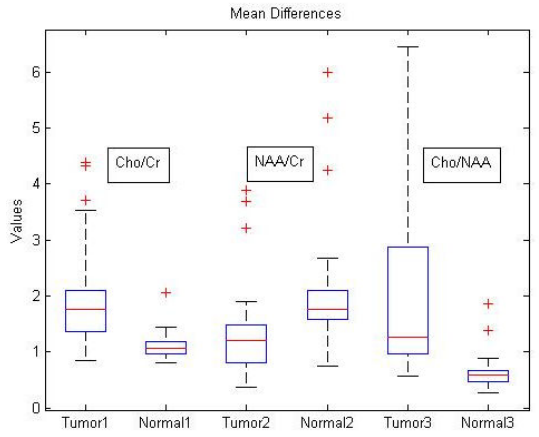

Fig. 2. Boxplot comparison of Cho/Cr (1), NAA/Cr (2), Cho/NAA (3) between Tumor and Normal tissues (+ represents outliers, the box lines represent the first quartile, median, and the third quartile and the whisker shows the whole range). The Cho/NAA and Cho/Cr ratios cover larger ranges while NAA/Cr include lower ones in tumor vs. normal tissues.

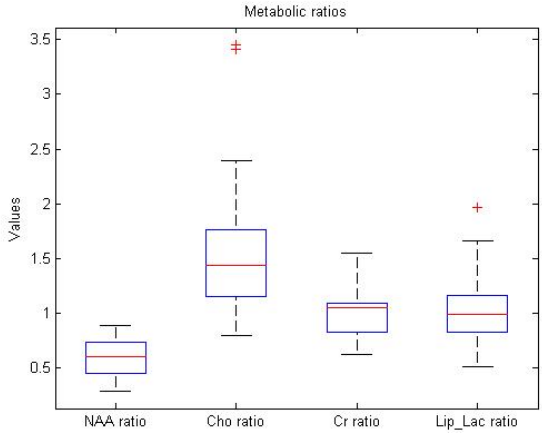

Fig. 3. Boxplots for NAA/contralateral NAA , Cho/contralateral Cho , Cr/contralateral Cr, Lip-Lac/contralateral Lip-Lac. (+ represents outliers, the box lines represent the first quartile, median, and the third quartile and the whisker shows the whole range). The increase of Cho (Cho ratio >1) and decrease of NAA (NAA ratio<1) in the tumor vs. contralateral normal tissue are shown while other metabolites do not offer good discriminations (range around 1).

As shown in Table II, Cho/Cr and Cho/NAA were statistically significant (P-value<0.001) in differentiation of tumor from normal tissues while NAA/Cr was not discriminative (P-value = 0.105). According to Table II, the odds of tissue being tumor and having Cho/Cr>1.10, NAA/Cr<2.08, and Cho/NAA>0.63 are 11.87, 3.28, and 19.12 times the odds of tissues being normal and having those conditions respectively. In Fig. 3, the Boxplots show the MRSI ratio features (NAA, Cho, Cr, and Lip-Lac) of the detected tumors to their contralateral normal tissues. Note that the Cho/Contralateral-Cho was mostly higher than 1 and the NAA/contralateral-NAA was lower than 1 confirming the increase of Cho and decrease of NAA in the tumor. The others cover a range around 1 and are not discriminative.

IV. Discussion

An unsupervised classification method was developed to segment abnormal regions based on the MRSI features. It was applied to metabolite ratios of 20 brain tumor patients. The detected tumor regions corresponded to their locations on the anatomical images. The MRSI ratios were in good agreement with those reported in the literature. It was shown that Cho/NAA was the best feature for the discrimination of tumor from normal tissues. The advantage of this method is that it does not need any training and can detect four different kinds of tumor on real data. However, it failed to detect the presence of necrosis and some low grade tumors.

TABLE II
ODD RATIOS AND P-VALUES FROM 3 DISCTINCT LOGISTIC REGRESSION MODELS IN DIFFERENTIATION OF ABNORMALITIES FROM NORMAL TISSUES. THE CHO/CR AND CHO/NAA WERE STATISTICALLY SIGNIFICANT IN DISCRTIMINATION OF TUMOR FROM NORMAL TISSUES WHILE NAA/CR WAS NOT. CHO/NAA WAS THE BEST DISCRIMINATOR (THE HIGHEST ODD RATIOS).

Ratio	Odd ratios	P- value
Cho/Cr>1.10	11.87	<0.001
NAA/Cr<2.08	3.28	0.105
Cho/NAA>0.63	19.12	<0.001

Recent investigations have proposed diagnosis of tumor characteristics using the combination of MRSI and Diffusion Tensor Magnetic Resonance Imaging (DTMRI) [6], [11]. DTMRI measures water diffusion anisotropy of a tissue. Apparent Diffusion Coefficient (ADC) is one of the DTI features that measures the diffusion of water in a tissue. It appears higher in low cellular regions like necrosis [14] and low grade tumors [11] than in high grade tumors [11]. Therefore, using DTI features like ADC in conjunction with MRSI features is expected to improve the performance of the proposed algorithm in the detection of low grade and necrosis tumors.

This method can be extended to cluster 3D data and measure the volume of abnormality, useful for brain surgery and radiation therapy.

V. Conclusion

MRSI is a noninvasive method which measures metabolites in the brain tissue. In this study, an unsupervised classification method was developed to detect a variety of brain tumors based on their MRSI features. The proposed method could detect four different kinds of tumor and the results were in agreement with investigation done independently by other groups. The Cho/NAA was the best feature for differentiating tumor from normal tissue. This is consistent with the expected increase of Choline (cellular proliferation) and decrease of NAA (axonal defects) in the tumors. It can be concluded that the MRSI metabolites have the potential to be used as biomarkers in the non-invasive diagnosis of the brain tumors.

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